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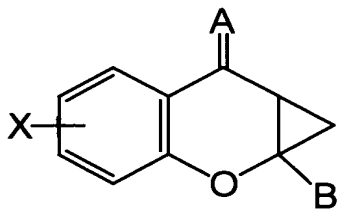
Partial translation of JP-A-8-169884

Translation of Claims and paragraphs [0001] to [0004]:

[Claims]

[Claim 1] A cyclopropachromenecarboxylic acid derivative represented by the following general formula (1)

[Chem. 1]



(1)

[wherein A represents oxygen atom, hydroxyimino group, an alkyloxyimino group having from 1 to 5 carbon atoms or a group $=N-O-(CH_2)_n-NR^1R^2$ (wherein n is an integer of from 2 to 8 and each of R^1 and R^2 independently represents hydrogen atom or an alkyl group having from 1 to 5 carbon atoms), B represents a group $-COOR^3$ (wherein R^3 represents hydrogen atom or an alkyl group having from 1 to 5 carbon atoms) or a group $-CONR^4R^5$ (wherein each of R^4 and R^5 independently represents hydrogen atom, an alkyl group having from 1 to 5 carbon atoms, an alkenyl group having from 2 to 5 carbon atoms, an aminoalkyl group in which the N may be substituted, phenyl group substituted with a

halogen atom or hydroxyl group which may be substituted, 2-pyridyl group or an aralkyl group having from 7 to 10 carbon atoms, or NR^4R^5 may together form a nitrogen-containing heterocyclic group which may be substituted), and X represents a halogen atom or a group $-OR^6$ (wherein R^6 represents hydrogen atom, an alkyl group having from 1 to 5 carbon atoms, an alkenyl group having from 3 to 6 carbon atoms or an aralkyl group having from 7 to 10 carbon atoms)] or a pharmacologically acceptable salt thereof.

[Claim 2] A therapeutic agent for various diseases caused by functional and/or organic disorders in the brain, which comprises a cyclopropachromenecarboxylic acid derivative represented by the general formula (1) of claim 1 or a pharmacologically acceptable salt thereof as the active ingredient.

[Detailed Description of the Invention]

[0001]

[Technical Field to which the Invention Belongs] This invention relates to novel cyclopropachromenecarboxylic acid derivatives and pharmacologically acceptable salts thereof. More particularly, it relates to novel cyclopropachromenecarboxylic acid derivatives and pharmacologically acceptable salts thereof, which have metabotropic glutamate receptor antagonism and are effective in improving and treating various diseases caused by functional and organic disorders in the brain, including

various symptoms caused by cerebral ischemic disorders such as aftereffects after cerebral infarction, after cerebral bleeding and after cerebral arteriosclerosis and other symptoms caused by various organic disorders induced by senile dementia, post-traumatic syndrome after head injury, secondary disease after brain operation, Alzheimer disease and Parkinson disease.

[0002]

[Prior Art] It is considered that abnormal activation of glutamate receptors caused by the excessive release of glutamic acid as an excitatory neurotransmitter in the living body is concerned in the progressive delayed neuronal cell death which is observed after brain injuries accompanied by head injuries and cerebrovascular diseases (cerebral bleeding, transient cerebral ischemia, cerebral infarction) [D.T. Monaghan *et al.*, *Annu. Rev. Pharmacol. Toxicol.*, 29, 365 (1989); B. Meldrum *et al.*, *Trends Pharmacol. Sci.*, 11, 379 (1990)]. Glutamate receptors are roughly classified into two types of ionotropic receptor (iGluR) which by itself has an ion channel function and a metabotropic receptor (mGluR) which communicates to intracellular signal transduction system via G protein [S. Nakanishi, *Science*, 258, 597 (1992)], and their antagonists have been researched and developed as drugs capable of preventing or inhibiting neuronal cell death. However, most of them are iGluR antagonists [J.C. Watkins *et al.*,

Trends Pharmacol. Sci., 11, 15 (1990); D. Lodge *et al*, ibid., 11, 81 (1990)], and only L-AP3 [D. Schoepp *et al.*, *Trends Pharmacol. Sci.*, 14, 13 (1993)] and a phenylglycine derivative [Y. Hayashi *et al.*, *J. Neurosci.*, 14, 3370 (1994)] are known as mGluR antagonists whose concern in neuronal cell death has recently been suggested [D. Bleakman *et al.*, *Mol. Pharmacol.*, 42, 192 (1992); J.W. McDonald *et al.*, *J. Neurosci.*, 13, 4445 (1993)].

[0003]

[Problems that the Invention is to Solve] Under the above background, the problem to be solved by the invention is to provide a novel compound which has mGluR antagonism and is useful as a drug for improving or treating functional and organic disorders in the brain.

[0004]

[Means for Solving the Problems] The present inventors have previously found that a cyclopropachromene derivative shows a brain protecting action under a reduced pressure low oxygen condition and have applied the result for a patent (JP-A-4-235180; the term "JP-A" as used herein means an "unexamined published Japanese patent application"). Thereafter, paying attention to mGluR, particularly to its subtype mGluR1 conjugated with hydrolysis of inositol phospholipid [M. Masu *et al.*, *Nature*, 349, 760 (1991)] and using rat mGluR1 expressing CHO cells [S. Nakanishi *et al.*, *Neuron*, 8, 757 (1992)], the inventors have conducted

extensive synthesis studies using, as an index, an antagonism for intracellular calcium ion increase induced by glutamic acid and found that a carboxylic acid derivative of cyclopropachromene has mGluR1 antagonism, thereby resulting in the accomplishment of the invention. Thus, the present invention provides, as a substance having mGluR1 antagonism, the following general formula (1)

Translation of paragraphs [0098] to [0101]:

[0098]

Evaluation Example 1. Evaluation of mGluR1 antagonism using intracellular Ca^{2+} response of mGluR1 expressing CHO cells as an index

Since mGluR1 (metabotropic glutamate receptor 1) induces release of Ca^{2+} from the intracellular Ca^{2+} storing region as an intracellular signal transduction system via the production of inositol 1,4,5-triphosphate, the mGluR1 antagonism can be evaluated using intracellular Ca^{2+} response in mGluR1-expressed cells as the index.

[0099]

By employing this evaluation system and using rat mGluR1-expressed CHO cells [S. Nakanishi *et al.*, *Neuron*, 8, 757 (1992)], the amount of intracellular Ca^{2+} induced by 10 μM of glutamic acid when compounds of the invention were

added in various concentrations was measured by a Fura-2-employed fluorometry [H. Sugino *et al.*, *Brain Res.*, 322, 127 (1984)], and the results were compared with the case of no addition of the test samples to evaluate antagonism of the compounds of the invention for mGluR1 using antagonism for the increase of intracellular Ca^{2+} as the index. As a result, all of the compounds of the invention showed antagonism for mGluR1, and as shown in Table 3, the compounds of Example Nos. 32, 34, 35, 36, 41, 42, 43 and 53 showed particularly strong antagonism with a 50% competitive inhibition concentration (to be referred to as IC_{50}) of 100 μM or less. The IC_{50} values of (S)-4CPG and MCPG [Y. Hayashi *et al.*, *J. Neurosci.*, 1 104, 3370 (1994)] used as control drugs were also shown in the table.

[0100] Table 3

Example No.	IC_{50} (μM)
32	23
34	20
35	3
36	10
41	100
42	100
43	20
53	100
(S)-4CPG	200
MCPG	700

[Effects of the Invention]

[0101]

According to the invention, novel carboxylic acid derivatives of cyclopropachromene and pharmacologically acceptable salts thereof having antagonism for metabotropic glutamate receptor can be provided. Since the compounds of the invention have antagonism for metabotropic glutamate receptor and also have low toxicity, their application is expected as medicaments for improving various diseases caused by functional disorders and organic disorders in the brain.